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EXAMINER	
HENLEY III, RAYMOND J	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,866	BROWN, DENNIS M.	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☒ Claim(s) *1,6 and 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/1/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 1-14 ARE PRESENTED FOR EXAMINATION

Applicant's Information Disclosure Statement filed September 1, 2004 has been received and entered into the application. As reflected by the attached, completed copy of form PTO/SB/08A, the Examiner has considered the cited references.

Claim Objections

Claims 1, 6 and 7 are objected to because of the following informalities:

In claims 1 and 7, the objectives of "treatment" (claim 1) and "prophylactic" (claim 7) are inconsistent with the function of the amount of the cephalotaxine, i.e., "in an amount *to inhibit...*"

Also, the expression "is administered" in claim 6 does not have antecedent basis in claim 1, where "contacting" is recited. Appropriate correction is required.

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the progression of an angiogenic disease, such as cancer, an inflammatory disease, (e.g., rheumatoid arthritis, osteoarthritis, asthma and/or pulmonary fibrosis), diabetic retinopathy or macular degeneration, does not reasonably provide enablement for a method of prophylactic treatment or inhibiting the onset, (i.e., interpreted to mean complete inhibiting of such onset, i.e., preventing) the above diseases/disorders.

Also, while the specification is enabling for the treatment of an angiogenic disease or inhibiting the progression of an angiogenic disease, such as cancer, an inflammatory disease, (e.g., rheumatoid arthritis, osteoarthritis, asthma and/or pulmonary fibrosis), diabetic retinopathy or macular degeneration, the specification does not reasonably provide enablement for the presently claimed methods which lack a positive recitation of a therapeutic objective to be attained in the claimed hosts.

For both of the issues presented above, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Examiner has noted the variety of conditions to which Applicant has claimed prophylactic treatment or the inhibition of the onset using the claimed compound. For the purposes of consideration under 35 U.S.C. § 112, first paragraph, the Examiner has focused on the specific angiogenic diseases cancer and inflammation. However, the reasons stated here concerning the non-enablement of preventing cancer and inflammatory diseases apply also to the genus of angiogenic diseases as claimed, but for the obvious difference in the type of disorder.

For the purposes of the present analysis under 35 U.S.C. § 112, first paragraph, the terms "prophylactic" and "inhibiting the onset" have been given their broadest reasonable interpretation (see MPEP § 2111) to mean that the angiogenic disease is kept from ever occurring in a patient to any degree, i.e., absolute absence of the disease process. The term "prevent", including grammatical variations thereof, will be used herein to refer to the claimed "prophylactic" and "inhibiting the onset" objectives.

The burden of enabling diseases, such as the claimed angiogenic diseases, which include

such conditions as cancer and inflammation, would be much greater than that of enabling the treatment or inhibition of the progression of such conditions. Given the unusual status of absolute prevention in the art, it is deemed highly unlikely, and the Office would require experimental evidence to support the contention, that the claim specified compounds could actually prevent an angiogenic disease by simply administering, using any known method, an amount of the claim specified active agents.

The term "preventing" is synonymous with "curing" and both circumscribe methods of treatment having absolute success. Because even with the treatment, much less prevention, of "common" diseases/conditions, absolute success cannot be reasonably expected, the present specification, which lacks an objective showing that prevention can actually be accomplished, is viewed as lacking an adequate enabling disclosure for the prevention of angiogenic diseases.

The Examiner recognizes that an actual working example is not required to satisfy the requirements of 35 U.S.C. § 112, first paragraph. However, because for the reasons to follow, the Examiner has reason to doubt the accuracy of the statements in the specification that angiogenic diseases can actually be prevented, the presence of such an example would obviate the present point of rejection.

As set forth in *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contain therein which must be relied on for enabling support*; assuming that sufficient reason for such doubt exists, *a rejection for failure to teach how to make and/or use will be proper on that basis*, such a rejection can be overcome by suitable proofs indicating that teaching contained in specification is truly enabling." (emphasis added).

Here, the objective truth of the statement that a an angiogenic disease could actually be prevented is based on the teachings of Hawk et al. (Hematology/Oncology Clinics reference) which teaches throughout at pages 809-826 that cancer therapy is not developed to the point where prevention can be predicted or expected with a reasonable degree of certainty.

For example, Hawks et al. teach that "Nevertheless, a brief review of the proceedings from the 1984 workshop reveals that the challenges involved in translating *the promise of cancer prevention* into a clinical reality remain and indeed may now be even more complex" (emphasis added), (page 809, above the heading "Neoplasia-Process Versus Event"). Also, in the paragraph bridging pages 825-6 it is disclosed that "[t]he tools are now available to make prevention of cancer a clinical reality. As the science of prevention *improves*, it must be remembered that effective and efficient preventive services do not help if they are not used." (emphasis added). Also, in a prophetic manner, the authors further teach at the last sentence on page 826 that "[f]inally, the most effective cancer prevention program *will probably use* both rational drug therapy targeting specific risk factors and public health efforts to promote healthy lifestyle choices in the population at large."(emphasis added).

Also, at page 817, first full paragraph, Hawk et al. teach "The primary goal for prevention agents is to demonstrate reductions in a cancer of interest and in the morbidities and mortality associated with it. Beyond these straightforward goals, prevention also seeks to affect more complex clinical characterizations of benefit, such as quality of life, frequency or safety of screening and surveillance procedures, or effects across several chronic diseases (reference omitted). Indeed, it now seems that several promising chemopreventive agents...*may reduce the incidence of cancer* in several target organs or may have preventive or therapeutic effects against

several disease processes." (emphasis added).

Respect the presently claimed objective of preventing inflammation (present claims 11 and 12), such is doubted by the Examiner because Shen et al. (U.S. Patent No. 6,458,829, cited by the Examiner) teaches "At present there is no cure or prevention (prophylactic) available for rheumatoid arthritis, only regimens that address symptoms such as pain and stiffness", (see col. 3, lines 17-19).

That inflammation could be prevented is further doubted because as expressly recited in both claims 1 and 7, the amount of the cephalotaxine that is administered is sufficient to *inhibit* angiogenesis (claim1) or "the onset or progression of an angiogenic disease" (claim 7).

Further supporting the Examiner's doubt of the objective truth of the statement that a cephalotaxine compound could be effective for the prevention of an inflammatory disease or condition, is the state of the art concerning the pathogenesis of osteoarthritis, an inflammatory disease or condition. In particular, in Cecil, Textbook of Medicine at page 1550, col. 2, first paragraph under the heading "Osteoarthritis (Degenerative Joint Disease)", lines 12-14, it is taught that "Because *no treatment can currently prevent or ameliorate the basic disease process...*".

Thus, for the above reasons, the Examiner has met the burden as advanced by the court in *Marzocchi, Id.,* of providing the reasons why one would doubt the accuracy of the statements contained in the present specification that must be relied on by Applicant for enabling support.

Also, <u>all</u> of the present claims lack a recitation of a therapeutic objective to be achieved through the administration of the claimed active agents. This point of rejection may be overcome by specifying that the treatment is for an angiogenic disease. For example, claim 1

would be amended to read "A method of ~~treatment of~~ treating an angiogenic disease in a host with an angiogenic disease comprising contacting said host...".

The claims as filed are not limited to an objective of affecting any particular disease/condition. Therefore, the claims encompass the treatment of the host for *any* therapeutic purpose. The art, however, is currently unaware of any agent, or combination of agents, which is effective for treating all disease conditions, i.e., a panacea. Lacking knowledge of such, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that all disease conditions could be treated in a mammal taking a lipid profile modifying/lowering drug. Given that the art fails to recognize, and Applicant has failed to demonstrate, that all disease conditions could be treated in a mammal being administered a lipid modifying/lowering drug, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention.

The following references are relied upon in support of the Examiner's position: Kumar (cited by the Examiner, abstract only) teaches "The role of melatonin in organisms physiology has now been widely recognized, and the wealth of information accumulated in the past two decades indicate it to be the best hormone candidate to be investigated for a universal panacea." (penultimate and last line of the abstract); Oka et al. (cited by the Examiner, abstract only) teaches "At the present time, however, there is no single panacea. To achieve the maximum preventive and therapeutic effects with the minimum toxicity, two or more immunosuppressive drugs are used appropriately in combination, taking the mechanisms of action of each into consideration (penultimate and last line of the abstract); Smith et al. (cited by the Examiner,

abstract only) teaches "[hormone replacement therapy] is not a panacea for an unhealthy lifestyle." (line 11 of the abstract); and Rickels et al. (cited by the Examiner, abstract only) teaches "Anxiolytics are not a panacea, but only tools to allow the patient to help himself or herself." (lines 11-12 of the abstract).

Also, factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the appropriate factors from those above are applied to the present application (see below) and weighed, it is the examiner's position that the present specification would only enable the skilled artisan to inhibit the progression of an angiogenic disease.

(1) The nature of the invention/state of the prior art, relative skill of those in the art, the predictability in the art.

Claims 7-14 are directed to prophylactic treatment of a host comprising contacting said host with a cephalotaxine in an amount sufficient to inhibit the onset or progression of an angiogenic disease. Claims 1-14 fail to specify a particular therapeutic objective to be achieved through following the recited method steps. The relative skill of those in the art is high.

(2) The breadth of the claims

The claims do not recite a therapeutic objective to be achieved through the "contacting" of the claimed active agents with the claimed host. Also, while claim 7 recites that the

cephalotaxine is "contacted" in an amount sufficient to inhibit the progression of an angiogenic disease, the claim also includes the recitation that such amount is sufficient to inhibit the onset of the angiogenic disease. As noted previously by the Examiner, given its broadest, reasonable interpretation (see MPEP § 2111) such recitation of inhibiting the onset of an angiogenic disease may be interpreted to mean the complete inhibition of such onset, i.e., preventing

(3) The amount of direction or guidance presented and presence or absence of working examples.

The specification provides merely provides statements that a host may be "contacted" with the claimed active agents to accomplish the objective of "prophylactic treatment" (claim 7) and the claimed active agent may be administered in an amount sufficient to inhibit the onset of an angiogenic disease (claim 7). For the reasons presented above, it is believed that the skilled artisan would doubt that such objectives could be accomplished. Also, while at pages 14-17 of the present specification data is provided showing that homoharringtonine is effective for *inhibiting* blood vessel growth of the chorioallantoic membrane of fertilized chicken eggs, no experimental data is present that shows, in fact, that an angiogenic disease can actually be prevented.

Further, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of preventing an angiogentic disease in terms of (i) identifying a patient population in need of preventive therapy, (ii) identifying whether or not a given patient may already suffer from an angiogenic disease which has not become clinically evident, (i.e., if the patient already suffers from, but shows no clinical evidence of, the disease, the administration of the claimed active agent (a cephalotaxine, such as homoharringtonine) would

be an instance of treating the disease, rather than preventing, which connotes the absence of the disease), or (iii) how to determine, when a given patient fails to develop a particular angiogenic disease, whether that patient was ever really at risk for developing such disease or if the absence of a particular angiogenic disease was, in fact, the result of administering the claimed active agent, i.e., the present specification lacks guidance as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for preventing an angiogenic disease.

(4) The quantity of experimentation necessary.

Insofar as the skilled artisan would have no expectation that the claimed objectives, which include the prevention of angiogenic diseases, could actually be achieved by practicing the method disclosed by Applicant, an undue quantity of experimentation would be necessary to achieve such a goal.

(5) The State of the Art

From the teachings of art relied on, *supra*, it is shown that cancer and inflammation prevention has not yet sufficiently developed such that the skilled artisan would have been imbued with a reasonable expectation or certainty that such could be accomplished by the means proposed by Applicant.

Summary

As the cited art and discussion above establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that an angiogenic disease could be prevented. In order to actually achieve the prevention of such diseases, it is clear from the discussion above that the skilled artisan could not rely on

Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. Given that the art fails to recognize and Applicant has failed to demonstrate that any angiogenic disease could be prevented through the administration of the claimed cephalotaxine compounds, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Further confounding the skilled artisan would be the lack of predictability in the art. That is, as discussed above, angiogenic diseases such as cancer and inflammation, are not thought to be amenable to complete or absolute prevention through chemo-preventive measures. Accordingly, claims 1-14 are deemed properly rejected.

Claim Rejection - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 9 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention." (MPEP 2173).

The term "analog" in the expression "homoharringtonine analog" (claims 5 and 14) is a relative term which renders the claim indefinite. In particular, "analog" does not particularly

point out the degree or type of analogy that a given compound may have in relation to the parent compound and still be considered a "homoharringtonine analog" as intended by applicant.

Also, the term "micro" in the expressions "microtumor or micrometastatic cancer cells" is a term of degree as employed by applicant that encompasses an undefined range of cancer cell presence beginning with a single cancer cell up to some undefined value.

Applicant has failed to provide any specific definition or basis for determining the scope of either "analog" or "micro". Lacking a clear meaning of these terms, the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter for which Applicant seeks patent protection. Also, the public would not be informed of the boundaries of what constitutes infringement of the patent. Further supporting the examiner's position is the statement at page 7, line 19 of the present specification where "microtumors", along with the parentheses, is set forth. Such indicates that the term is qualified. The qualification, however, has not been explained by applicant.

Accordingly, the claims are deemed properly rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

It should be noted that because the Examiner has determined that claims 7-14 are not enabled, these claims have not been further rejected under 35 U.S.C. § 103.

I Claims 1 and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Powell et al. (U.S. Patent No. 3,793,454) in view of D'Amato (U.S. Patent No. 5,712,291) and Kawai et al. (Cancer Letters, 171 (2001) 201-207, cited by the Examiner).

Powell et al. teach a method of treating mice for remission of leukemic tumors of the strains L1210 and P388 which comprises administering to said mice, by intraperitoneal injection, an effective amount an active compound selected from harringtonine and isoharringtonine (see claim 1 at cols. 11-12).

It is further taught that an isolate of *C. harringtonia*, i.e., isolate 16, contained, *inter alia*, cephalotaxine (see present claim 4) and was effective against the leukemia when administered intraperitoneally, (see col. 3, lines 38-41 and 58-61 and Table 1). It is noted that the patentees teach that cephalotaxine, *per se*, has been shown to be inactive against L1210 and P388 strains of leukemia (col. 1, lines 53-54). However, the requirements of the present claims are nevertheless met because, as noted above, isolate 16 apparently contained a mixture of compounds which was effective against the leukemia. The present claims recite comprising and thus do not exclude this circumstance of administration.

The differences between the above and the claimed subject matter lies in that Powell et al. fail to teach that the leukemia strain is an angiogentic disease and is not a solid tumor. Also, the patentees fail to teach an "amount sufficient to inhibit angiogenesis" (see present claim 1).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because of the following reasons.

D'Amato teaches that "[i]t should be noted that angiogenesis has been associated with blood-born tumors such a leukemias, any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs...It is believed that angiogenesis plays a role in the abnormalities in the bone marrow that give rise to leukemic-like tumors." (col. 3, lines 23-31). Also, Kawai et al. teach "leukemic cells line, representative of a non-solid tumor" (see, for example, the abstract at page 201, line 6). Accordingly, for these reasons, it is believed that the skilled artisan would have appreciated the leukemia of Powell et al. to be a non-solid tumor and also be considered an angiogenic disease, thus meeting the requirements of the present claims.

Also, the actual dosage amounts which underlie the functional expression "amount sufficient to inhibit angiogenesis" is disclosed at page 10, lines 18-21 of the present specification to be broadly from 0.05 – 5.0 mg/m^2. In Powell et al., different units of measure are set forth in Table16 (col. 10) where a range of from 2 to 24 mg/kg/day is disclosed. The Examiner cannot readily determine the body surface area of the mice treated in Powell et al. However, because in Powell et al. amounts sufficient to treat the leukemia were administered, it is believed that such provides an adequate basis for concluding that the amounts required by the present claims are at least suggested by the patentees.

Accordingly, for the above reasons, the claims are deemed properly rejected.

II Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chinery et al. (U.S. Patent Application Publication No. 2001/0049349) in view of D'Amato (U.S. Patent No. 5,712,291), Cecil's Textbook of Medicine (pp. 1060-1074, cited by the Examiner), O'Dwyer et

al. (Journal of Clinical Oncology article, cited by the Examiner), Medford (U.S. Patent No. 5,380,747)

Initially, as will be appreciated from the following analysis, the problem addressed by Chinery et al., i.e., to enhance the cytotoxic activity of an antineoplastic drug (see the abstract, line 1), and Applicant, i.e., to treat angiogenic diseases, are not the same. However, "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991)" (MPEP § 2144 under the heading "Rationale Different From Applicant's is Permissible").

Chinery et al. teach a method for the treatment of abnormal cell hyperproliferative conditions which comprises administering to a host (see page 12, paragraph [0161]) effective amounts of an antioxidant (not excluded from the present claims which recite "comprising"[1]) and an antineoplastic agent, such as homoharringtonine (page 12, paragraph [0152], middle of the paragraph), (see page 12, paragraph [0154]).

The conditions which Chinery et al. teach as being amenable to treatment include rheumatoid arthritis (page 12, line 3 of paragraph [0157]; compare to present claims 2 and 3 where the inflammatory disease can be rheumatoid arthritis), "hematopoietic tumors such as

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[1] Should Applicant consider employing the phrase "consisting essentially of", MPEP § 2111.03 should be noted "For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, 'consisting essentially of' **will be construed as equivalent to 'comprising.'** See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ('PPG could have defined the scope of the phrase consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the

lymphoma, leukemia, plasma cell dyscrasias, and multiple meyloma and amylodosis" (page 12, last three lines of paragraph [0158]) and "cardiovascular proliferative disease such as post-angioplasty restenosis and atherosclerosis" (page 12, paragraph [0159]).

Chinery et al. further teach that the antioxidant can be administered in combination with the antineoplastic agent (page 13, lines 2, 4 and 5 of col. 1) and that the antioxidant may be administered via several routes including subcutaneously, intraperitoneally, intramuscularly, parenterally, orally, transdermally, (page 13, paragraph [0162]), intradermally and topically, (page 13, paragraph [0171]).

The differences between the above and the claimed subject matter lie in that Chinery et al. fail to teach:

(1) rheumatoid arthritis, leukemia and atherosclerosis as angiogenic and/or inflammatory diseases, (see present claims 1-3);

(2) that from the listing of antineoplastic agents at page 12, paragraph [0152], homoharringtonine, or "analogs" thereof, could be used specifically for leukemia, rheumatoid arthritis and/or atherosclerosis;

(3) intravescular and/or intraarterial as routes of administration, (present claim 6); and

(4) an "amount sufficient to inhibit angiogenesis" (present claim 1).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because of the following reasons:

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invention.'), (emphasis added).

(1) D'Amato provides teachings that would have led one of ordinary skill in the art to appreciate that rheumatoid arthritis, leukemia and blood-born tumors in general, and atherosclerosis are angiogenic diseases. In particular, D'Amato teaches "Another disease in which angiogenesis is believed to be involved is rheumatoid arthritis..." (see col. 2, lines 35-44); "Another pathological role associated with angiogenesis is found in atherosclerosis. The plaques formed within the lumen of blood vessels have been shown to have angiogenic stimulatory activity" (col. 2, lines 58-61); and "It should be noted that angiogenesis has been associated with blood-born tumors such as leukemias, any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs..." (col. 3, lines 23-31).

Also, Chinery et al. teach that atherosclerosis may be treated (page 12, paragraph [0159]. The requirements of present claim 2 would have been met and/or suggested thereby because at paragraph [0159], Chinery et al. indicate that atherosclerosis is associated with angiogenesis and thus may be reasonably interpreted as an angiogenic disease as in present claim 1. Also, Medford et al. expressly teaches "Adhesion of leukocytes to the endothelium represents a fundamental, early event in a *wide variety of inflammatory conditions, including atherosclerosis*..." (col. 1, lines 11-14).

Because Chinery et al. teach that the above diseases may be treated with the combination of an antioxidant and an antineoplastic agent, such as homoharringtonine, such teaching would have motivated one of ordinary skill to carry out such treatments.

(2) The choice of a specific antineoplastic agent to employ for the treatment of cancer is dependent on the type of cancer. That is, there is no one particular antineoplastic agent, or

combination thereof, which is known to be effective for the treatment of each and every type of cancer known. In this respect, note Cecil's Textbook of Medicine (pp. 1060-1074). One of ordinary skill in the art would have been motivated to select homoharringtonine from the listing of antineoplastic agents disclosed by Chinery et al. at page 12, paragraph [0152] because homoharringtonine was known to be effective against leukemias and lymphoma (see O'Dwyer et al., see the first paragraph on page 1563 and the paragraph bridging pages 1563-4, especially the middle of that paragraph on page 1564, "In vitro testing of [homoharringtonine] against ten human leukemia or lymphoma lines showed a 70-fold difference in growth inhibition between the most sensitive and the most resistant lines. Those with a high growth fraction tended to be most sensitive to HHT.". Therefore, high growth fraction leukemias and lymphomas would have been reasonably expected to be amenable to treatment with homoharringtonine.

With respect to the other conditions, i.e., those conditions that are not cancers, taught by Chinery et al. at page 12, paragraphs [0153] – [0154], it appears that the invention of Chinery et al. is to treat any of such diseases with any of the listed antineoplastic agents. Thus, because homoharringtonine is identified as an antineoplastic agent, and antineoplastic agents, in combination with an antioxidant, are taught to be effective for the inflammatory disease rheumatoid arthritis (paragraph [0157]), one of ordinary skill in the art would have been motivated to use of homoharringtonine for the treatment of rheumatoid arthritis, i.e., an angiogenic disease as explained, *supra*.

Applicant's claim 2 requires "an inflammatory disease" while claim 3 specifies rheumatoid arthritis. One of ordinary skill in the art would have recognized rheumatoid arthritis from the express teaching of Chinery et al. of "the chronically inflamed state of rheumatoid

arthritis" (col. 2, lines 43-44). Also, atherosclerosis would have been encompassed by present claim 2 because it was known as an inflammatory disease, (as well as an angiogenic disease as discussed above).

(3) Chinery et al. teach parenteral administration in general and thus would have motivated one of ordinary skill in the art to select any specific parenteral route of administration.

(4) Also, the actual dosage amounts which underlie the functional expression "amount sufficient to inhibit angiogenesis" (present claim 1) is disclosed at page 10, lines 18-21 of the present specification to be broadly from 0.05 – 5.0 mg/m^2. In Chinery et al., the specific dosage amounts for the antineoplastic agents have not been disclosed. However, because in Chinery et al. amounts sufficient to treat rheumatoid arthritis, leukemia and atherosclerosis are implicitly taught, it is believed that such provides an adequate basis for concluding that the amounts required by the present claims are at least suggested by the patentees.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Provisional Obviousness-Type

I Claims 1-6 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15-17 of copending Application No. 10/617,927. Although the conflicting claims are not identical, they are not patentably distinct from each other because present claims 1-6 contain at least each element of the co-pending claims, expect for an administration period of from 5 to 25 days per month.

Claim 15 is representative of the co-pending claims and reads:

"A method of treatment comprising administering the composition of claim 12, (i.e., a composition comprising homoharringtonine produced by an extraction method involving a *Cephalotaxus* plant), wherein said composition is administered by intravenous administration for 5 to 25 days per month".

The present claims provide for "contacting" or administration in general. The administration of the present homoharringtonine composition for a period of from 5 to 25 days per month would have been readily obvious to one of ordinary skill in the art.

"Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)" (see MPEP 2144.05(II)). The determination of the optimum period of administration would have been expected to vary and to have been made in accordance with a variety of factors. These would

have included such factors as the severity of the condition and the responsiveness of the patient to be treated.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

II Claims 1-6 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over either of (i) claims 1 and 16-21 of co-pending Application No. 10/769,638, or (ii) claims 15-20 of co-pending application Serial No. 10/631,106. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons.

Representative of the claims of the '638 application is claim 1 which reads:

> 1. (currently amended) A method of treatment of a host with a cellular proliferative disease, comprising contacting said host with a composition comprising a cephalotaxine homoharringtonine [cephalotaxine, 4-methyl-2-hydroxy-2-(4-hydroxy-4- methyl pentyl) butanedioate (ester),] and an antiproliferative agent camptothecin, each in an amount sufficient to modulate said cellular proliferative disease.

The claims of the '106 application are substantially similar except that instead of homoharringtonine being co-administered with camptothecin, amonafide is administered.

The claim sets are not patentably distinct because:

(1) the present claims recite "comprising" and thus do not exclude the additional active agent of either the '638 or '106 application; and

(2) the co-pending claim sets are directed to "a cellular proliferative disease" which would include the angiogenic disease which is not a solid tumor of the present claims where the disease is leukemia.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Accordingly, for the above reasons, the claims are deemed properly rejected.

The references cited on the attached form PTO-892 and not relied on by the Examiner are included to show the general state of the art.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J. Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Raymond J Henley III
Primary Examiner
Art Unit 1614

July 30, 2005